BOTANICAL MEDICINES TO SUPPORT HEALTHY SLEEP AND REST

Note: Please refer to the <u>Passport to Whole Health</u>, Chapter 15 on Dietary Supplements for more information about how to determine whether or not a specific supplement is appropriate for a given individual. Supplements are not regulated with the same degree of oversight as medications, and it is important that clinicians keep this in mind. Products vary greatly in terms of accuracy of labeling, presence of adulterants, and the legitimacy of claims made by the manufacturer.

Botanical medicine (herbalism or herbal medicine) has been practiced for millennia in many different cultures, with the earliest documented use of herbal medicine being 5000 years ago in China and India.[1] As with any type of medicine, both risks and benefits exist.

In contrast to synthetic medications which usually contain one or perhaps two active ingredients, herbal treatments usually contain dozens or hundreds of bioactive compounds that may serve to modify the response or to reduce toxicity. This is one reason that clinical trials that isolate one putative active ingredient of an herbal treatment often find it to be ineffective. In contrast to drugs, herbals treatments are generally gentle and exert biological effects over longer periods of time than typical drug treatments do. Therefore, short randomized controlled trials (RCT's) of herbal remedies, adapted from clinical trial methodology for drugs, are also often negative. Despite these issues, 80% of the total world population, and 95% of the developing world, uses herbal medicines.[2] Whether they are guided by folk knowledge or have consulted an herbalist, they are often forced to evaluate a bewildering number of products, claims and labels without the benefit of any professional advice, especially in the US. The intent of this tool is to help clinicians have enough background to offer such advice when it comes to supplements that support healthy energy levels and high quality sleep.

NERVINES

"Nervine" is the term used in botanical or herbal medicine for herbs that are believed to act on the nervous system. Nervines are most often consumed in the form of a tea, although other formulations (e.g. tinctures) are also available. Nervines can be classified as nervine stimulants, nervine relaxants, and nervine tonics.

NERVINE STIMULANTS

Nervine stimulants are widely consumed throughout the US and the world. Although we seldom think of our morning coffee in this way, coffee is, in fact, a strong water-based extract made from the dried and roasted beans of *Coffea Arabica*. The main active ingredient in this nervine, caffeine, is well studied pharmacologically, and it is a potent adenosine antagonist. Adenosine is thought to mediate the homeostatic, or "Process S"

sleep drive. This drive describes how the pressure to sleep increases linearly from the time of the last sleep period.[3] Coffee is a good example of how a natural intervention in the form of a nervine stimulant can safely and effectively address a sleep-related symptom, sleep inertia, or somnolence due to inadequate sleep.

This is not to say that caffeine does not have toxicity, but when one considers that in the US alone, more than 400 million cups of coffee are consumed *each day*,[4] and that worldwide, more than 2.25 billion cups of coffee are consumed daily[5] with few reported fatalities for coffee overconsumption[6], the margin of safety is reassuring. Imagine how that would compare to stimulant medications like amphetamine or methylphenidate. In addition to caffeine, coffee contains many other bioactive compounds, including flavonoids that may offer benefits that cannot be obtained from simply taking caffeine tablets.

However, caffeine is almost certainly overused in our society, and it contributes greatly to insomnia and sleep complaints.[7] Even in individuals without sleep complaints, the consumption of a single cup of coffee in the morning has measurable effects on sleep parameters. One recommendation that a health provider might feel comfortable making is that patients substitute green tea (*Camellia sinensis*) for at least some of the coffee they habitually consume.

In addition to having much less caffeine than coffee, green tea also contains high levels of various antioxidant flavonoids called catechins that may offer benefits including treating cardiovascular diseases, controlling body weight, increasing bone mass, protecting against neurodegenerative diseases and improving type 2 diabetes.[8] Tea contains high levels of theanine as well. Theanine is a non-protein amino acid that appears to enhance dopamine release and result in inhibition of excitatory neurotransmission, thus acting as an anxiolytic.[9]

NERVINE RELAXANTS

Nervine relaxants are also widely used worldwide (although nowhere near as frequently as coffee) to reduce tension, anxiety, and sleep disturbance. Many of these agents may have benefits that cross over to other organ systems. For example, chamomile (*Matricaria recutita*), one of the most common nervine relaxants, is helpful for insomnia, but also is useful for a nervous stomach. Unfortunately, similar benefits cannot be attributed to pharmaceutical sleeping medications. Specific nervine relaxants include the following:

German chamomile (*Matricaria recutita*). German Chamomile is one of the most widely used and versatile medicinal plants. It can be used as an infusion of the dried flowers or ethanolic extract. To prepare, pour 1 cup of boiling water over 2-3 heaping teaspoons (2-4 grams) of dried herb. Alternatively one can use 30-40 drops of a 1:5 45% alcoholic tincture, or take a solid extract as a 300-400 milligrams capsule. Taking a 200 milligram Chamomile extract capsule once daily for 28 days has been shown to significantly improve sleep quality in the elderly[10]. Another study demonstrated that taking 220-1100 milligrams of chamomile extract once daily for 8 weeks significantly decreased generalized

anxiety[11]. Chamomile may be taken thirty minutes prior to bedtime or three times daily for gastrointestinal (GI) symptoms.

Lemon balm (*Melissa officinalis*). Lemon balm has been used since the Middle Ages for anxiety and insomnia. It is often combined with other agents. In vitro studies have suggested that lemon balm is effective by acting as a GABA agonist[12]. It is available as a dried herb and in extracts and tinctures. To prepare a tea, steep ¼ to 1 teaspoon (1.5-4.5 grams) of dried herb per cup of hot water. Capsules are taken at doses of 300-500 milligrams up to three times a day. The dose for a tincture is up to 60 drops daily. For insomnia and anxiety, one effective dose of a lemon balm extract is 300 milligrams twice daily for 15 days.[13] Another study showed that 1200 milligrams of lemon balm extract once daily helped decrease the stress and tension related to premenstrual dysphoric disorder.[14]

Valerian (*Valerian officinalis*). Valerian may be unique among insomnia remedies in that it may work better for insomnia with longer-term administration. Remind patients who choose to take it that this is the case; they may find it works better if they have been taking it for a few weeks. It is thought to work by increasing GABA levels in the brain. Valerian is available as a raw herb, but the odor is likened to that of an old goat or sweaty socks, so if it is consumed as a tea, it is often combined with other agents, in part to mask the stink. To make a tea, a person can pour 1 cup of boiling water over 1 teaspoon of dried herb and drink 5-10 minutes before bedtime. Alternatively, take 1 to 1.5 teaspoon of a 1:5 tincture or .5 to 1 teaspoon of a 1:1 fluid extract before bed. As a dry extract, 250-600 mg capsules before bed are also available. Many studies have suggested that 400-900 milligrams of valerian root extract up to 2 hours before bedtime has been helpful for insomnia.[15]

Hops (*Humulus lupulus*). Hops are another widely used nervine relaxant. The flowering strobiles of the female hops plant contain high concentrations of active principles humulone and lupulone that remain present in the dried herb. The usual dose is 0.5 grams of the dried herb prepared as a tea or as a dry extract. Hops are thought to interact with melatonin receptors, and they are often combined with other agents such as valerian. Currently, available evidence suggests that a combination product including hops and valerian may improve sleep latency as compared to a placebo after 28 days of treatment.[16] At this point in time evidence in support of hops use in improving sleep quality is mixed, and there are no available studies about the effects of hops when used as a monotherapy.[17]

Kava kava (*Piper methysticum*). Kava kava has been traditionally used by indigenous peoples of the South Pacific. It is derived from the rhizomes of the kava shrub. Some of the health benefits of kava are known to be due to agents called kavapyrones, also known as kavalactones. Kava kava is a potent sedative and sleep-promoting agent. It has the potential for both hepatic and neurological toxicity with long-term use, and has actually been banned in some countries because of liver-related concerns. Kava is poorly soluble in water, so ethanol-water or acetone water extracts are typically used. Because of the potential for toxicity it is perhaps best not to routinely recommend its use. Clinicians who do suggest it often follow up with liver function lab tests. It is often included in

multicomponent herbal sleep remedies, so careful label reading is essential. A recent systematic review suggested that kava may be beneficial for short term use (4-8 weeks) in the setting of generalized anxiety disorder. Recommended dose is 120-280 milligrams per day of Kavalactones.[18]

NERVINE TONICS

Nervine tonics, unlike nervine stimulants or nervine relaxants, have no parallel in modern pharmacotherapeutics. Nervine tonics are thought to nourish and support the nervous system. One might think of them as restoring balance. The mechanisms of action are probably heterogeneous. Examples of this class of herbal remedies include the following:

Milky oats (*Avena sativa*). Milky Oats are prepared by expressing the juices of immature oats. The fluid is then made into a tincture. The customary dose is 20-40 drops 4 times a day. Milky oats are described as a nervous system restorative and nutritive tonic.[19] It is traditionally recommended for those who give and give until they are themselves depleted.

Skullcap (*Scutellaria lateriflora*). Dried areal parts of this common weed can be made into a tea. Flavonoid constituents are weak GABA agonists[12]. Other components bind serotonin receptors, but it is unclear whether they have an agonist or antagonist effect. Skullcap may be taken as an extract 1-2 grams daily. To prepare a tea, once can use 1-2 grams of dried herb steeped in 150 milliliters of boiling water for 5-10 minutes and then strain. According to Natural Medicines Comprehensive Database, adulteration with other scutellaria species can be a problem; there are many plants that are referred to as skullcap. Stick with reputable herbal suppliers and products. To date, there have been two clinical trials that have shown use of Skullcap to be correlated to a sense of relaxation and an overall mood improvement.[20,21] The former study used a single dose of organic freezedried extract dosed between 100-350 milligrams, and the later study used 350 milligrams of freeze-dried extract 3 times daily for 2 weeks.

St. John's Wort (*Hypericum perforatum*). St. John's Wort has been an herbal treatment for more than 2000 years. Paracelsus (1493-1541) described its use to treat depression. Multiple studies have compared St. John's Wort (SJW) to standard antidepressants and have found it to be as effective as tricyclic antidepressants (TCAs) and serotonin-specific reuptake inhibitors (SSRIs) in mild to moderate depression.[22] However, SJW is subject to multiple drug interactions, particularly through cytochrome 450 3A4 inhibitory effects. This supplement must be used with caution, and clinicians should familiarize themselves with specific interactions and use caution whenever a person could be taking it concomitantly with medications. Used with the guidance of an experienced herbalist or other practitioner, SJW may be a reasonable alternative to conventional antidepressants for mild to moderate depression. The usual dose is 300 milligrams 3 times a day for 6 weeks, standardized to 0.3% hypericin content.[23]

ADAPTOGENS

Adaptogens are a class of botanicals that have been in traditional use for thousands of years. They were extensively studied and developed in the Soviet Union as a means to help soldiers, athletes and even cosmonauts adapt to stress. Much of the data regarding these agents was classified and has been made available only since the dissolution of the Soviet Union. Adaptogens likely have multiple mechanisms of action, including bolstering the hypothalamic-pituitary (HPA) axis and providing weak cholinesterase inhibition. With acute stress, the HPA responds by releasing elevated levels of stress hormones, including cortisol. With chronic stress, the end organ—the adrenal glands—may become less able to respond in what is sometimes referred to as adrenal fatigue or exhaustion. (Refer to the "Adrenals" tool.)

Sleep is often affected in both the acute and exhausted phase of the stress response. Adaptogens may be useful along with mind-body interventions to improve the resilience of the HPA in the face of acute and chronic stress, and as a result, they may improve sleep. Improved sleep is, of course, key in promoting hippocampal neurogenesis, an important step in HPA regulation.

Adaptogens can be used as single agents or combinations. Proprietary extracts are also used. A few examples are offered below; refer to the "Adaptogens" tool for additional details.

Ginseng. Multiple botanicals are referred to as "ginseng." Three of the most popular in the United States are American Ginseng (*Panax quinquefolius*), Korean ginseng (*Panax ginseng*) and Siberian Ginseng (*Eleutherococcus senticosus*), which is now required by law in the US not to be referred to as ginseng. All three herbs have been used as adaptogens. There is evidence that they may work by lowering elevated cortisol levels, and they also may lower post-prandial blood glucose in type 2 diabetes. Although Korean ginseng has been used to improve athletic performance, data supporting a benefit are lacking. Data are stronger for the use of Korean ginseng for erectile dysfunction. The main active ingredients of Korean ginseng, ginsenosides, have multiple potential actions. One recent study showed that Korean ginseng taken 24 hours after intense physical activity helped decrease muscle damage and HPA axis responses to this physical stress.[24] Dosing is highly variable depending on the therapeutic aim.

Ashwagandha (*Withania somnifera*). Ashwagandha is a classical herb of Ayurveda (traditional Indian healing; refer to the "Ayurveda" section in Chapter 18 of the *Passport to Whole Health*) that is classified as a *rasayana* or rejuvenating herb. Like ginseng, it tends to lower elevated cortisol levels. Central nervous system effects may include decreasing stress-induced elevations in striatal dopamine, and ashwagandha seems to improve several markers of immune function as well. The typical dose is 1-6 grams of whole herb a day. A tea may be prepared by boiling the herb in water for about 15 minutes. The tea is cooled and then consumed 3-4 times throughout the day. Some evidence has pointed to triethylene glycol, a component of Ashwaganda leaves, as an inducer of non-REM sleep.[25]

Rhodiola (*Rhodiola rosea*). Rhodiola is also known as golden root, andhas been used as a dietary herb and in traditional medicine in northern Europe and Asia for over 3000 years. It is felt to improve stamina and athletic performance. Rhodiola's potential biological actions are complex. There is some data to support its use in generalized anxiety disorder. One randomized controlled trial showed self-reported improvement of anxiety, depression, mood, confusion, stress and anger after 14 days using a Rhodiola extract. [26] Dosing depends on the indication and the specific proprietary extract. According to the Natural Medicines Comprehensive Database, the Rhodiola extract from Germany (Finzelberg, GmbH) has been dosed as 200 milligrams for a single dose or 100 milligrams twice daily. For depression, a specific Rhodiola extract (SHR-5) at 340 milligrams once daily or 340 milligrams twice daily has been studied. That same extract has been used for improving fatigue at doses of 50 milligrams twice daily, 170 milligrams daily, or a single dose of 370-555 milligrams. Side effects include agitation, insomnia, increased anxiety and palpitations. Because Rhodiola is mildly stimulating it should be used with caution in bipolar patients.

SUMMARY

Some of the most commonly-used used herbals for sleep are listed in the section below with their respective doses and side effects.

HERBALS FOR INSOMNIA AND ANXIETY

Chamomile

- Uses: Sedative, "nervous stomach"
- Approximate Daily Doses: 2-4 grams in tea
- Side Effects: Not for people with ragweed allergy

Lemon balm

- Uses: Mild sedative
- Approximate Daily Doses: 600 milligrams
- Side Effects: None

Valerian

- Uses: Anxiety, insomnia
- Approximate Daily Doses: 450-900 milligrams
- Side Effects: Morning sedation and headache rare

Theanine

- Uses: Mild anxiety
- Approximate Daily Doses: 200 milligrams
- Side Effects: May interact with Coumadin

St. John's Wort

- Uses: Depression
- Approximate Daily Doses: 300-600 milligrams three times daily
- Side Effects: Drug interactions significant

Rhodiola

- Uses: Adaptogen
- Approximate Daily Doses: 50-900 milligrams
- Side Effects: Rare agitation

Adapted from Brown, refer to the resources below.

RESOURCES

- Brown R, Gerbarg P, Muskin P. How to Use Herbs, Nutrients and Yoga in Mental Health Care. New York, NY: W.W. Norton; 2009
 - Useful information on using complementary approaches in mental health care.
- Low-Dog, T. *Healthy at Home: Get Well and Stay Well Without Prescriptions.* Washington, DC: National Geographic Press; 2014
 - A treasure trove of information on herbal treatments but also a beautifully written and accessible treatise on the philosophy of integrative medicine.
- Natural Medicines Comprehensive Database website
 - o A tremendous dietary supplement resource. Mobile apps are also available.
- Schulz V, Hansel R, Tyler V. *Rational Phytotherapy: A Reference Guide for Physicians and Pharmacists*. New York: Springer; 2004
 - o Helpful detailed reference on commonly used herbals.

AUTHOR(S)

"Botanical Medicines to Support Healthy Sleep and Rest" was written by <u>Vincent Minichiello</u>, MD, (2018). Sections were adapted from "A Natural Approach to Sleep, Stress, and Insomnia" by <u>John W. McBurney</u>, MD.

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REFERENCES

- 1. Rivera J, Loya A, Ceballos R. Use of herbal medicines and implications for conventional drug therapy medical sciences. *Altern Integr Med.* 2013;2(6).
- 2. Robinson MM, Zhang X. *Traditional medicines: global situation, issues and challenges.* WHO Geneva;2011.
- 3. Manber R, Carney CE. *Treatment plans and interventions for insomnia: A case formulation approach.* New York, NY: The Guilford Press; 2015.
- 4. Kitchen Daily. America's Coffee Obsession: Fun Facts that Prove We're Hooked. http://www.huffingtonpost.com/2011/09/29/americas-coffee-obsession n 987885.html. Updated February 27. 2015. Accessed October 22, 2018.
- 5. Ponte S. The 'Latte Revolution'? Regulation, markets and consumption in the global coffee chain. *World Development.* 2002;30(7):1099-1122.
- 6. Mowry JB, Spyker DA, Brooks DE, Zimmerman A, Schauben JL. 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. *Clin Toxicol (Phila)*. 2016;54(10):924-1109.
- 7. National Sleep Foundation. Caffeine and sleep. 2018; http://www.sleepfoundation.org/sleep-topics/caffeine-and-sleep. Accessed October 22, 2018.
- 8. Pastoriza S, Mesias M, Cabrera C, Rufian-Henares JA. Healthy properties of green and white teas: an update. *Food Funct.* 2017;8(8):2650-2662.
- 9. Lardner AL. Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders. *Nutr Neurosci.* 2014;17(4):145-155.
- 10. Adib-Hajbaghery M, Mousavi SN. The effects of chamomile extract on sleep quality among elderly people: A clinical trial. *Complement Ther Med.* 2017;35:109-114.
- 11. Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ, Shults J. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract therapy for generalized anxiety disorder. *J Clin Psychopharmacol.* 2009;29(4):378-382.
- 12. Savage K, Firth J, Stough C, Sarris J. GABA-modulating phytomedicines for anxiety: A systematic review of preclinical and clinical evidence. *Phytother Res.* 2018;32(1):3-18.
- 13. Cases J, Ibarra A, Feuillere N, Roller M, Sukkar SG. Pilot trial of Melissa officinalis L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. *Med J Nutrition Metab.* 2011;4(3):211-218.
- 14. Akbarzadeh M, Dehghani M, Moshfeghy Z, Emamghoreishi M, Tavakoli P, Zare N. Effect of Melissa officinalis capsule on the intensity of premenstrual syndrome symptoms in high school girl students. *Nurs Midwifery Stud.* 2015;4(2):e27001.
- 15. Natural Standard Database. Valerian.

 https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=870. Updated 6/15/2018. Accessed 10/17/2018.
- 16. Morin CM, Koetter U, Bastien C, Ware JC, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep.* 2005;28(11):1465-1471.

- 17. Natural Standard Database. Hops. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=856. Updated 6/1/2018. Accessed 10/17/2018.
- 18. Ooi SL, Henderson P, Pak SC. Kava for generalized anxiety disorder: A review of current evidence. *J Altern Complement Med.* 2018;24(8):770-780.
- 19. Hoffman D. *Medical herbalism: The science and practice of herbal medicine.* Rochester, VT: Healing Arts Press; 2003.
- 20. Wolfson P, Hoffmann DL. An investigation into the efficacy of Scutellaria lateriflora in healthy volunteers. *Altern Ther Health Med.* 2003;9(2):74-78.
- 21. Brock C, Whitehouse J, Tewfik I, Towell T. American Skullcap (Scutellaria lateriflora): a randomised, double-blind placebo-controlled crossover study of its effects on mood in healthy volunteers. *Phytother Res.* 2014;28(5):692-698.
- 22. Apaydin EA, Maher AR, Shanman R, et al. A systematic review of St. John's wort for major depressive disorder. *Systematic Reviews.* 2016;5(1):148.
- 23. Natural Standard Database. St. John's Wort. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=329. Accessed 10/17/2018.
- 24. Flanagan SD, DuPont WH, Caldwell LK, et al. The effects of a Korean ginseng, GINST15, on hypo-pituitary-adrenal and oxidative activity induced by intense work stress. *J Med Food.* 2018;21(1):104-112.
- 25. Kaushik MK, Kaul SC, Wadhwa R, Yanagisawa M, Urade Y. Triethylene glycol, an active component of Ashwagandha (Withania somnifera) leaves, is responsible for sleep induction. *PLoS One.* 2017;12(2):e0172508.
- 26. Cropley M, Banks AP, Boyle J. The effects of Rhodiola rosea L. extract on anxiety, stress, cognition and other mood symptoms. *Phytother Res.* 2015;29(12):1934-1939.